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Original Research Article

Quantitative analysis of diffusion weighted imaging in rectal cancer during radiotherapy using a magnetic resonance imaging integrated linear accelerator

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ABSTRACT

Background and purpose: Magnetic resonance imaging integrated linear accelerator (MR-Linac) platforms enable acquisition of diffusion weighted imaging (DWI) during treatment providing potential information about treatment response. Obtaining DWI on these platforms is technically different from diagnostic magnetic resonance imaging (MRI) scanners. The aim of this project was to determine feasibility of obtaining DWI and calculating apparent diffusion coefficient (ADC) parameters longitudinally in rectal cancer patients on the MR-Linac.

Materials and methods: Nine patients undergoing treatment on MR-Linac had DWI acquired using b-values 0, 30, 150, 500 s/mm^2. Gross tumour volume (GTV) and normal tissue was delineated on DWI throughout treatment and median ADC was calculated using an in-house tool (pyOsirix ®).

Results: Seven out of nine patients were included in the analysis; all demonstrated downstaging at follow-up. A total of 63 out of 70 DWI were analysed (7 excluded due to poor image quality). An increasing trend of ADC median for GTV (1.15×10^{-3} mm^2/s interquartile range (IQ): 1.05–1.17 vs 1.59×10^{-3} mm^2/s IQ: 1.37 – 1.64; $p = 0.0156$), correlating to treatment response. In comparison ADC median for normal tissue remained the same between first and last fraction (1.61×10^{-3} mm^2/s IQ: 1.56–1.71 vs 1.67×10^{-3} mm^2/s IQ: 1.37–2.00; p = 0.9375).

Conclusions: DWI assessment in rectal cancer patients on MR-Linac is feasible. Initial results provide foundations for further studies to determine DWI use for treatment adaptation in rectal cancer.

1. Introduction

Management of locally advanced rectal adenocarcinoma includes neo-adjuvant chemoradiotherapy (nCRT) to rectum and pelvic nodes followed by surgery [1,2]. Pathological complete response (pCR) is seen in 15–25% [3] following nCRT, which improves 5-year overall survival (OS) in these patients to >87% [4] compared to 50–60% in those who do not achieve pCR [5,6]. Achieving pCR or tumour regression grade (TRG) 0–2 [7] in rectal cancer is shown to be an independent prognostic factor for OS, local recurrence, and disease free survival [4,5,8–10], and a 'watch and wait' policy of delaying surgery until the first signs of recurrence is advocated in these patients [11–13] under strict imaging surveillance [14].

To improve pathological response to nCRT dose escalated treatment at >60 Gy to gross tumour volume (GTV) is required [15]. However, increasing dose to tumour comes with worsening toxicity to normal tissue [16], and consequently a fine balancing act is required between improving tumour response and limiting long-term morbidity. Image guided radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT) reduces dose delivered to organs at risk (OARs) such as small bowel [17,18]. Using magnetic resonance imaging integrated linear accelerator (MR-Linac) platforms online adaptations to treatment can be made based on anatomy of the day further improving dose delivery to tumour whilst sparing normal tissue [19].

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Magnetic resonance imaging (MRI) also provides the added benefit of giving functional information about tumour biology in the form of diffusion weighted imaging (DWI). High intensity signal on DWI corresponds to malignant tissue [20] and reduction of signal relates to disruption of cell membrane integrity thus suggesting regression of tumour caused by treatment [21]. Several studies have been published demonstrating ability to stratify rectal cancer patients into good and poor responders using pre-treatment DWI and apparent diffusion coefficient (ADC) [22–26], with good responders exhibiting an earlier response to treatment compared to the poor responders [27]. Recognising poor responders early in treatment could potentially allow for treatment adaptation with dose escalation in order to achieve pCR [28].

However, these finding are not successfully reproduced in the majority of studies and DWI is yet to be validated as an imaging biomarker in this setting [29]. Furthermore, reproducing the methodology of DWI across studies is difficult due to use of different diagnostic MRI scanners and varying sequencing protocols [30]. Acquiring multiple MRI scans during treatment is also not feasible in a busy clinical department [21], therefore simultaneously scanning and treating the patient on an MR-Linac overcomes this hurdle [31] providing a means of investigating real time biological changes in tumour [32].

The design of one such MR-Linac differs from diagnostic MRI scanners [31] and causes technical difficulties in obtaining DWI at higher b-values [33]. As such, the quality of images obtained on this MR-Linac in rectal cancer longitudinally throughout treatment is not known and requires assessment. The aim of this study was to demonstrate feasibility and clinical relevance of DWI obtained in rectal cancer patients treated on an MR-Linac.

2. Material and methods

2.1. Patients and treatment

Patients with a locally advanced rectal cancer (stage ≥T3, nodal involvement, circumferential margin (CRM) involvement, presence of extramural vascular invasion (EMVI) or threatened levators) [2], tumour size <12 cm, suitable for nCRT and with no contraindications to MRI and suitable for MR-Linac treatment or imaging were recruited to research and ethics commitee approved institutional based studies for treatment and imaging (PERMIT trial (NCT03727698) and PRIMER trial (NCT02973828)). Staging investigations such as CT and MRI, colonoscopy and biopsy were undertaken in local hospitals prior to referral to our unit. All patients' treatment pathways were discussed in central multidisciplinary meeting. Patients were treated with nCRT with concurrent Capecitabine 825 mg/m^2 BD or Raltitrexed 3 mg/m^2 day 1 every 21 days if Capecitabine was contraindicated. A two-phase radiotherapy protocol was delivered; Phase 1 boost to gross tumour volume (GTV) and nodes delivering 9 Gy/5# on MR-Linac (delivered first due to longer duration of daily treatment on MR-Linac which symptomatic patients may not tolerate in last week of radiotherapy) followed by Phase 2 treatment to pelvis via C-arm Linac delivering 45 Gy/25# to GTV plus mesorectum and pelvic nodes. Response to treatment was assessed 8–12 weeks post-treatment with follow-up diagnostic MRI and/or histopathology following surgery using TRG response [7].

2.2. Pre-treatment planning

Patients treated on MR-Linac underwent a planning CT scan (Philips, Big Bore CT) and MR simulation scan either on diagnostic MRI (Siemens, Aera 1.5T) or MR-Linac (Elekta Unity, 1.5 T). Bladder filling protocol on MR simulation required patients to empty bladder and drink 700 mls of water 1 h prior to scanning. Scanning was performed in treatment position, ideally with an empty rectum. If rectum ≥5 cm on initial planning scan patients were re-scanned following bowel preparation. Radiotherapy planning was performed on Monaco® v5.40.01 (Elekta AB, Stockholm, Sweden) for Phase 1 and Raystation® v10.0.1.52 (RaySearch Laboratories AB, Stockholm, Sweden) for Phase 2.

2.3. Imaging acquisition on MR-Linac

Imaging on MR-linac included T2 weighted 2 min scans utilised for online adaptation as described previously [34,35], followed by research imaging including DWI sequences. DWI acquisition was in keeping with consensus guidelines [33] and included diffusion weightings b = 0, 30, 150, 500 s/mm^2 combined to make 4D DWI (Fig. 1). Table 1 demonstrates sequencing parameters for acquisition of rectal DWI on MR-Linac. DWI was acquired daily during phase 1 and weekly during phase 2.

2.4. Quantitative analysis

Between Jan 2018 and Dec 2020, nine patients were consecutively recruited for nCRT on MR-Linac. DWI was not obtained in the first two patients therefore these patients were excluded from the analysis. Demographics of the remaining seven are shown in Table 2. All patients demonstrated a TRG 1–3 response following treatment as assessed by MRI or histopathology following surgery.

For each patient, ten DWI were acquired during treatment. 7/70 DWI were excluded from analysis as either DWI was not performed or not centred on tumour; thus 63 DWI were analysed in total.

DICOM images were imported into an open-source medical image viewer (Horos, GNU Lesser General Public License, Version 3 (LGPL-3.0)) where DWI were evaluated and GTV delineation on DWI was performed by a single experienced observer to minimise intra-observer delineation variability.

Utilising an in-house plug in tool (pyOsirix® [36,37]) ADC maps were created from b-values 150 and 500 s/mm^2. Contours for GTV and normal tissue (ovary for female, seminal vesicles for male), delineated on b = 500 s/mm^2 image, were transposed from DWI onto ADC map. Ovary and seminal vesicles chosen as normal tissue example as these organs were within planning tumour volume (PTV) and received same dose as GTV. ADC median for region of interest (ROI) at each fraction was calculated using in house-tool. Statistical analyses and graph modelling was performed using GraphPad Prism v9.1.2.

3. Results

An area of low ADC value was present on ADC maps corresponding to region of signal on b = 500 s/mm^2, which can be considered to demonstrate presence of tumour (Fig. 2a). All patients demonstrated a trend of increasing ADC median from fraction 1 (1.15×10^{-3} mm^2/s interquartile range (IQ): 1.05–1.17) to fraction 30 (1.60×10^{-3} mm^2/s IQ: 1.37–1.64) (Fig. 2b). Using Wilcoxon *t*-test the difference in ADC median between fraction 1 and 30 was found to be statistically significant (p = 0.0156). In comparison ADC median calculated in normal tissue showed no difference between first and last fraction (1.61×10^{-3} mm^2/s IQ: 1.56–1.71 vs 1.67×10^{-3} mm^2/s IQ: 1.37–2.00; p = 0.9375) (Fig. 2c). %ΔADC median calculated at weekly intervals demonstrates 3 patients (patients 4, 5 and 6) experiencing a >50% ΔADC from baseline by week 3, whilst 2 patients (patients 2 and 7) remain < 50%ΔADC from baseline throughout treatment (Fig. 3). There was no histopathological correlation to these trends.

4. Discussion

The findings from this study hold promise for utilisation of DWI signal and ADC metrics for adaptation of treatment according to treatment response on MR-Linac. Preliminary work on the longitudinal analysis of DWI and ADC median in rectal cancer on the MR-Linac demonstrated that an increase in ADC median in GTV is seen in all patients, whereas ADC median in normal tissue remains at similar value. ADC median of GTV also increases to a value comparable to normal

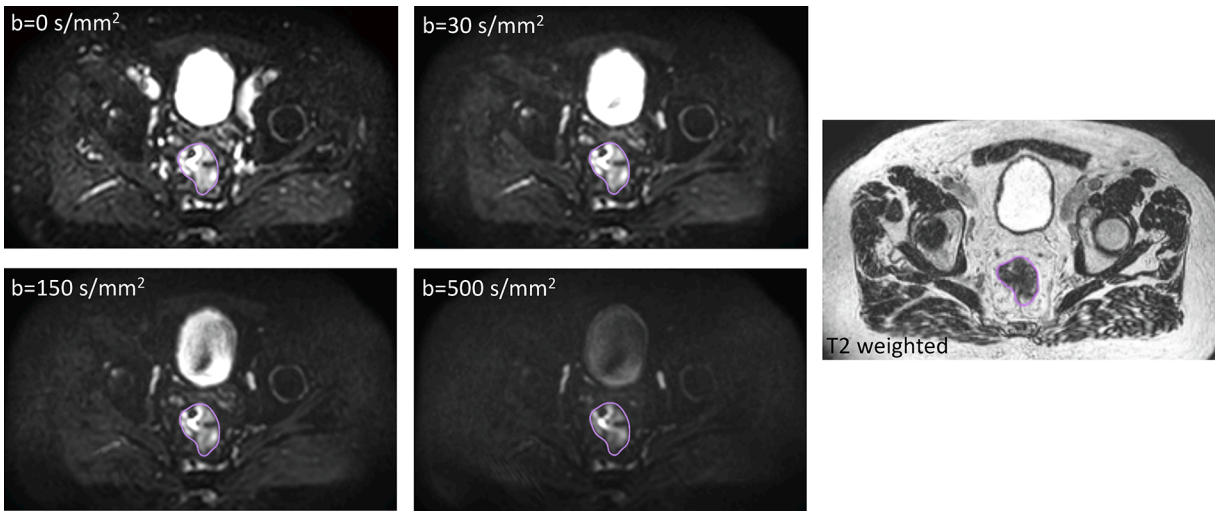

Fig. 1. Diffusion weighted images b = 0, 30, 150 and 500 s/mm^2 and T2 weighted image at first fraction of a patient with an upper rectal cancer tumour with GTV contour (purple).

Table 1
MRI sequencing parameters for DWI acquisition on Elekta Unity MR-Linac.

Parameters	Rectal DWI sequencing
Field of view (mm)	AP = 420
	RL = 420
	FH = 120
Recon. Voxel (mm)	
AP	1.75
RL	1.75
TR (ms)	4483
TE (ms)	81
DELTA/delta (ms)	40.7/20.3
Fat Suppression	STIR
EPI factor	55
Parallel imaging factor	2.2
Section thickness (mm)	4
Direction of motion probing gradients	Isotropic
b-factors (s/mm^2)	0, 30, 150, 500
b-factor averages	
b = 0	8
b = 30	8
b = 150	8
b = 500	16

Table 2
Patient and tumour characteristics.

		N = 7
Gender	Male	6 (86%)
	Female	1 (14%)
Age		61.3 yrs (Range 37–74)
T stage	T3a	1 (14%)
	T3b	1 (14%)
	T3c	3 (43%)
	T4	2 (29%)
N Stage	N1	5 (71%)
	N2	2 (29%)
M Stage	M0	7 (100%)
CRM involved	Yes	5 (71%)
	No	2 (29%)
EMVI present	Yes	7 (100%)
Mandard response post treatment	TRG 1	3 (43%)
	TRG 2	2 (29%)
	TRG 3	2 (29%)

tissue. Given that all patients demonstrated a pathological response TRG 1–3 to treatment, we suggest that Median ADC measured on MR-Linac appears to correlate to treatment response, which is in keeping with published literature [24,38]. These results are similar to a study performed on 0.35 T MR integrated platform looking at DWI in 3 patients [39].

Based on published evidence in rectal cancer, the principal parameter that predicts treatment response is %ΔADC (which compares post-treatment ADC metrics to pre-treatment ADC metrics calculated 6–8 weeks after completion of treatment) where patients with pCR demonstrate a >50% ΔADC compared to patients who do not achieve pCR [25,26,40,41]. However, we have observed that in five out of seven patients %ΔADC is <50% by the last fraction. One explanation is that the final DWI that we analyzed was obtained during the final week of RT as opposed to 6–8 weeks post-treatment as stated in the published studies. It is well known that tumour regression can continue following completion of CRT [42]. In addition, the signal intensity in the tumour is reduced by the end of treatment, leading to smaller volume of ROI for ADC calculations which can result in inaccuracies in ADC measurements [41].

Sun et al demonstrated a significant increase in ADC metrics and %Δ ADC during treatment where down-staged patients (TRG 1–3) had an earlier increase in ADC metrics by end of week 1 (1.07×10^{-3} mm/s^2 ± SD 0.13 pre-treatment to 1.32×10^{-3} mm/s^2 ± SD 0.16; $p < 0.001$) at end of week 1 and larger change in %ΔADC by end of week 2 (28.2% vs 9.8%; $p < 0.01$) compared to non-downstaged patients (TRG 4–5) [27]. Our results demonstrated three out of seven patients exhibit similar early rises in Median ADC and large %ΔADC by week 3 (fig, 2c and 3). However on further analysis based on TRG stratification, it was difficult to demonstrate a difference in trend between good (TRG 1–2) and poor responders (TRG 3–5).

Our study is limited by small patient numbers; therefore, further studies with larger patient numbers are required to demonstrate correlation between DWI measurements and pathological outcome in order to establish DWI as an imaging biomarker in clinical practice. We also recognise that combining ovary and seminal vesicles within normal tissue ROI may not give true representation of median ADC within normal tissue; however as these organs are included in the PTV and receive same dose as GTV it was deemed that this comparison was the most similar. Furthermore, assessing repeatability is also required if utilising DWI for patient stratification in order to ensure that ADC metric changes are due to treatment related changes in tumour biology, and not machine or other patient related factors [32].

Previous analysis of our data included b-values <100 s/mm^2 in ADC

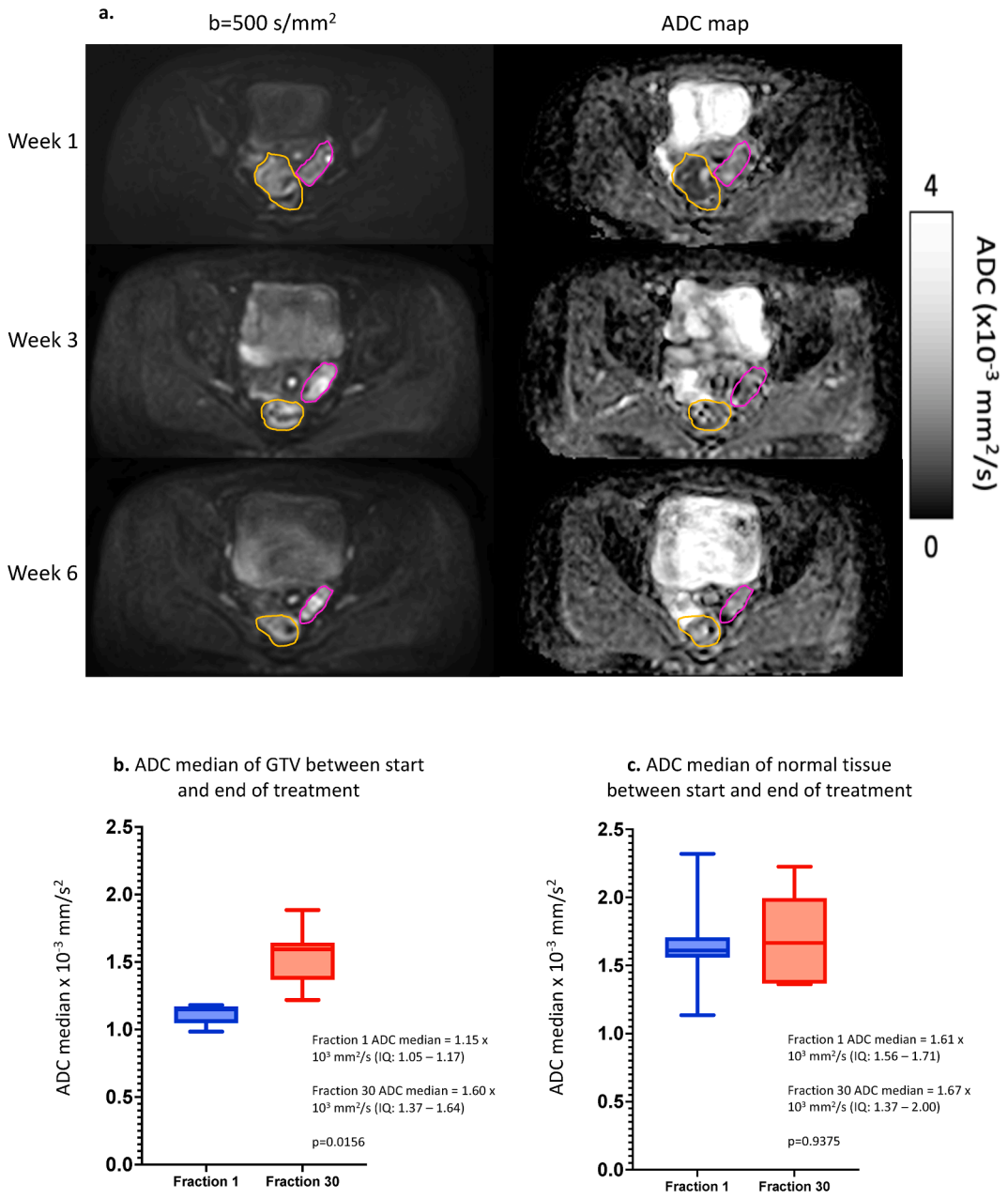

Fig. 2. a. Example of b = 500 s/mm^2 images and corresponding ADC maps from week 1, 3 and 6 of patient with an upper rectal tumour (orange contour) and ovary (pink contour). An area of low ADC value is seen in week 1 corresponding to area of high signal seen on DWI in GTV. b. Median ADC of tumour between first and last fraction, with an increasing trend seen. c. Median ADC of normal tissue between first and last fraction, with no change seen.

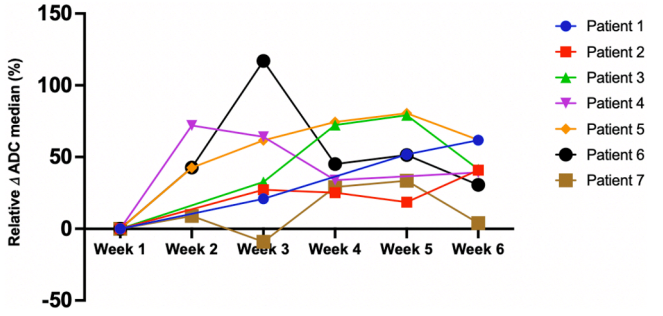

Fig. 3. Graph indicating relative ΔADC median (%) from baseline at weekly intervals.

calculations where we demonstrated one patient with a decreasing trend of ADC metrics [43]. Excluding b-values <100 s/mm^2 reversed this trend, indicating that lower b-values make ADC a more sensitive biomarker, especially to perfusion [33]. Intra-voxel incoherent motion (IVIM) analysis may provide more accurate assessment of tumour response to treatment by separating perfusion and diffusion factors [44], giving a more robust picture of tumour microcellularity during treatment.

In conclusion, DWI signal change and ADC metrics can be measured on MR-Linac in rectal cancer, demonstrating promise in its ability to determine response to treatment. Integration of DWI in adaptive radiotherapy planning may increase confidence in delivering dose escalated radiotherapy to GTV with the aim of improving treatment related outcomes in rectal cancer patients.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SL reports travel and educational grants from Elekta (Elekta AB, Stockholm, Sweden). SH reports non-financial support from Elekta (Elekta AB, Stockholm, Sweden), non-financial support from Merck Sharp & Dohme (MSD), personal fees and non-financial support from Roche outside the submitted work. SB reports travel and educational grants from Elekta (Elekta AB, Stockholm, Sweden)..

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